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Asymmetric epoxidation of α,β -unsaturated ketones catalyzed by chiral ytterbium complexes

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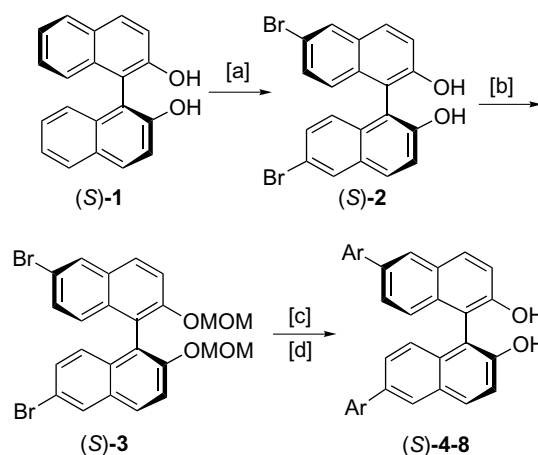
Abstract—Several derivatives of (*S*)-(-)-BINOL ligands with 6,6'-substituents were synthesized and applied as chiral ligands in the Yb(O-*i*-Pr)₃-catalyzed asymmetric epoxidation of α,β -unsaturated ketones. Superior results were obtained with 6,6'-diphenyl-BINOL, exemplified in the asymmetric epoxidation of (*E*)-1,3-diphenylprop-2-en-1-one in 91% yield and up to 97% ee. © 2001 Elsevier Science Ltd. All rights reserved.

The catalytic asymmetric epoxidation of α,β -enones has received much attention during the past few years.^{1,2} Recent developments include the use of molecular oxygen and diethylzinc in the presence of (*R,R*)-*N*-methylpseudoephedrine³ or optically active polybinaphthyl derivatives.⁴ Achiral alkyl peroxides, in conjunction with optically active (+)-diethyltartrate as a chiral auxiliary, resulted in good enantioselectivities.⁵ The Shibasaki catalyst, which is generated from an equimolar mixture of (*R*)-(+)-1,1'-2-naphthol (BINOL) and La(O-*i*-Pr)₃, can catalyze the asymmetric epoxidation of a range of (*E*)-enones in the presence of 4 Å molecular sieves.^{6a} In this case, chalcone was epoxidized in 93% chemical yield and 83% ee using cumene hydroperoxide (CMHP) as an oxidant. Ytterbium catalysts were found to give good enantioselectivities with alkyl α,β -enones. The effect of water on the ytterbium catalyst was also investigated;^{6b} 96% ee was obtained by Inanaga^{6c} after external addition of triphenylphosphine oxide (15 mol%). However, this became a multi-component catalytic system, which made the reaction conditions more complicated.

We envision that introduction of substituents on the 6,6'-positions of BINOL might have a profound effect on the activity and enantioselectivity as both the electronic and steric properties^{7–10} of the catalyst will be influenced. We have found that (*S*)-6,6'-diphenyl-

BINOL is a very efficient chiral ligand in the lanthanoid-catalyzed epoxidation of chalcone; up to 97% ee could be achieved, which is the highest ee value for epoxychalcone reported so far.

A series of 6,6'-disubstituted BINOL ligands were synthesized in the following manner (Scheme 1). (*S*)-BINOL **1** was brominated (Br₂ in CH₂Cl₂, -78°C) to give (*S*)-6,6'-dibromo-1,1'-bi-2-naphthol **2** in 98% yield. After converting the hydroxyl groups into MOM-



Scheme 1. Preparation of BINOL-derived ligands. *Reagents and conditions:* (a) Br₂, -78°C, CH₂Cl₂; (b) NaH, ClCH₂OCH₃, rt; (c) ArMgBr, Ni(PPh₃)₂Cl₂, Et₂O, reflux; (d) trace HCl, MeOH.

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ethers, aryl groups were introduced by cross coupling with an aryl Grignard reagent, catalyzed by $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ in Et_2O . Hydrolysis of the MOM-ethers with HCl/MeOH completed the synthesis of (*S*)-**4–8**. The total yields of the corresponding ligands of (*S*)-**4–8** are listed in Table 1. The chiral ytterbium catalysts were successfully prepared from ligands (*S*)-**1, 2, 4–8** by reacting them with $\text{Yb}(\text{O-}i\text{-Pr})_3$ in THF in the presence of MS 4 Å. The exact nature of the catalyst is still under investigation. It was found that an almost 1:1 ratio of $\text{Yb}(\text{O-}i\text{-Pr})_3$ and ligand (*S*)-**4** afforded the maximum enantiomeric excesses.

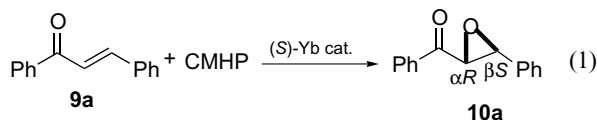
Chalcone **9a** was selected as the representative example to study. The reaction of **9a** with cumene hydroperoxide (CMHP) was carried out as described in Eq. (1) and the results are summarized in Table 2.

It is obvious that the 6,6'-disubstituents on BINOL have a remarkable effect on the enantioselectivity of the asymmetric epoxidation reaction. Using simple (*S*)-

Table 1. Total yields for the ligands of (*S*)-**4–8**

Entry	Ligand (Ar)	Yield (%)
1	(<i>S</i>)- 4 (Ph)	71
2	(<i>S</i>)- 5 (<i>p</i> -MeC ₆ H ₄)	64
3	(<i>S</i>)- 6 (<i>p</i> -MeOC ₆ H ₄)	45
4	(<i>S</i>)- 7 (<i>p</i> -CF ₃ C ₆ H ₄)	67
5	(<i>S</i>)- 8 (1-Naphthyl)	33

Table 2. Ligand optimization in $\text{Yb}(\text{O-}i\text{-Pr})_3$ -catalyzed asymmetric epoxidation of chalcone^a



Entry	Ligand	Yield (%)	Ee (%) ^b
1	(<i>S</i>)- 1	95	44
2	(<i>S</i>)- 2	76	62
3	(<i>S</i>)- 4	91	95
4	(<i>S</i>)- 4	90	95 ^c
5	(<i>R</i>)- 4	90	95 ^d
6	(<i>S</i>)- 4	91	97 ^e
7	(<i>S</i>)- 4	91	93 ^f
8	(<i>S</i>)- 5	78	70
9	(<i>S</i>)- 6	86	83
10	(<i>S</i>)- 7	88	89
11	(<i>S</i>)- 8	84	63

^a Reaction conditions: $\text{Yb}(\text{O-}i\text{-Pr})_3$ (5 mol%), Yb:ligand = 1:1; CMHP (150 mol%), $t = 8$ h, rt, THF.

^b Determined by HPLC (chiral OD column), absolute configuration was determined to be (α_R, β_S).

^c Ligand recovered after one experiment.

^d (*R*)-**4** was used.

^e 0°C, 36 h.

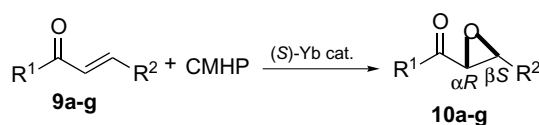
^f TBHP used instead of CMHP.

BINOL ((*S*)-**1**) as the ligand, the epoxy ketone **10a** was isolated in a low ee of 44% (Table 2, entry 1). (*S*)-**2**, which has bromine atoms on the 6,6'-positions of the phenyl, led to a moderate ee of 62% (Table 2, entry 2), although it exhibited a more promising optical induction in the enantioselective Strecker-type reactions of aldimine.¹¹ However, introduction of aryl substituents onto the 6,6'-positions of BINOL, induced much better enantioselectivity. Among all the ligands tested, (*S*)-**4** showed the highest enantioselectivity, with up to 95% ee obtained at room temperature (Table 2, entry 3). The same major (–)-enantiomer was formed in all cases. Comparison of the sign of the optical rotation with the literature data¹² revealed that the (–)-enantiomer of the epoxy ketone possessed the α_R, β_S configuration.

In order to further improve the enantioselectivity of the reaction, we have examined the effect of solvents and the reaction temperature. It was found that solvents strongly influence the degree of enantiomeric excesses,¹³ though the absolute configuration remains the same. THF gave the best result at room temperature. This may be ascribed to its ability to coordinate with the rare earth metal. The same results were obtained when (*R*)-**4** was used in place of (*S*)-**4**. Ligand (*S*)-**4** could be recovered and reused without any loss of yield or ee. (Table 2, entry 5). Lower reaction temperatures led to an improvement in enantioselectivity, although at the expense of reaction rate. That is, at 0°C the chalcone could be epoxidized with 5 mol% Yb catalyst in 97% ee and 91% isolated yield after 3 days (Table 2, entry 6). In addition, the use of *tert*-butyl hydroperoxide (TBHP) instead of CMHP did not improve the asymmetric epoxidation, giving the product with 93% ee in 91% yield (Table 2, entry 7), which is in contrast to the results reported by Shibasaki.^{6a} Moreover, the addition of both water and triphenylphosphine oxide to the Yb-**4** catalyst system resulted in no further improvement in the ee value.

The scope and the potential of the epoxidation of α, β -unsaturated ketones catalyzed by $\text{Yb}(\text{O-}i\text{-Pr})_3$ -(*S*)-6,6'-diphenyl-BINOL was further demonstrated by reacting a range of α, β -unsaturated ketones under optimized reaction conditions. The results are summarized in Table 3. It is clear that the nature of the substituents R^1 and R^2 of the enones has a great influence on the enantioselectivity of the epoxidation. Enones with aromatic substituents could be epoxidized in higher enantiomeric excesses than alkyl-substituted enones, which gave a lower ee value (Table 3, entry 6). In addition, when *o*-MOMOC₆H₄ was used instead of Ph as the olefinic substituent (R^1), the ee value decreased to 47%.

In conclusion, the ytterbium complex generated from $\text{Yb}(\text{O-}i\text{-Pr})_3$ and (*S*)-6,6'-diphenyl-BINOL in THF was found to be an efficient catalyst for the asymmetric epoxidation of α, β -unsaturated enones with cumene hydroperoxide. The best results were obtained for (*E*)-1,3-diphenylprop-2,3-epoxy-1-one with up to 97% ee in 91% chemical yields.

Table 3. Asymmetric epoxidation of enones with Yb(O-*i*-Pr)₃-(S)-**4**^a

Entry	Enone	R ¹	R ²	Epoxide	Yield (%)	Ee ^b (%)
1	9a	Ph	Ph	10a	95	95
2	9b	Ph	<i>p</i> -MeC ₆ H ₄	10b	83	54
3	9c	Ph	<i>p</i> -MeOC ₆ H ₄	10c	85	54
4	9d	Ph	<i>p</i> -ClC ₆ H ₄	10d	85	53
5	9e	Ph	<i>o</i> -MeOC ₆ H ₄	10e	81	66
6	9f	Ph	CH ₃ CH ₂ CH ₂	10f	85	38
7	9g	<i>o</i> -MOMOC ₆ H ₄	Ph	10g	88	47

^a Reaction conditions: Yb cat. 5 mol%, CMHP, 8 h, rt, THF.^b Determined by HPLC (chiral OD column), absolute configuration was determined to be (αR,βS).

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- The use of THF gave the best result (cf.: hexane, 4% ee in 77% yield; toluene, 81% ee in 89% yield; Et₂O, 82% ee in 83% yield; CH₂Cl₂, 73% ee in 90% yield).